profile comprises *measurements of said one or more sets of cellular constituents* (emphasis added). The first and second plurality of perturbations can be the same or different. Support for the amendment is found in the specification at page 23, line 15 through page 28, line 25; page 41, line 16 through page 43, line 30; and page 44, lines 28-29. In particular, the Examiner's attention is directed to page 41, lines 21-23 and page 44, lines 28-29. Claim 1 has also been amended to more particularly point out that the plurality of response profiles comprises at least five response profiles. Support for the amendment is found in the specification at page 15, lines 4-8.

Dependent claim 3 has been amended to depend on claim 1 so that there is proper antecedent basis. Dependent claim 6 has been amended to recite "said first plurality of perturbations" so that there is proper antecedent basis. Dependent claim 19 has also been amended accordingly so that there is proper antecedent basis.

Claim 29 has been amended to more particularly point out that the claimed method is for determining a consensus profile for a first plurality of perturbations by identifying *one or more sets of cellular constituents, each of said one or more sets of cellular constituents being upregulated or downregulated by said first plurality of perturbations* and that the consensus profile comprises *projected measurements of said one or more sets of cellular constituents* (emphasis added). Support for the amendment is found in the specification at page 23, line 15 through page 28, line 25; page 35, line 25 through page 36, line 30; page 39, line 5 through page 41, line 13; page 41, line 16 through page 43, line 30; and page 44, lines 28-29.

Dependent claims 30, 31 and 32 have been amended accordingly so that there is proper antecedent basis.

Claim 38 has been amended to more particularly point out that the claimed method is for determining a consensus profile for a first plurality of perturbations by identifying *one or more sets of genes, each of said one or more sets of genes being upregulated or downregulated by said first plurality of perturbations* and that the consensus profile comprises *measurements of transcript levels for said one or more sets of genes* (emphasis added). Support for the amendment is found in the specification at page 23, line 15 through page 28, line 25; page 41, line 16 through page 43, line 30; and page 44, lines 28-29.

Claim 39 has been amended to more particularly point out that in the claimed method the consensus profile comprises *projected measurements of one or more sets of cellular constituents, each of said one or more sets of cellular constituents being upregulated or*

downregulated by a first plurality of perturbations (emphasis added). Support for the amendment is found in the specification at page 23, line 15 through page 28, line 25; page 35, line 25 through page 36, line 30; page 39, line 5 through page 41, line 13; page 41, line 16 through page 43, line 30; and page 44, lines 28-29.

Claims 44, 100 and 72 have been amended to more particularly point out that the plurality of response profiles comprises at least five response profiles. Support for the amendment is found in the specification at page 15, lines 4-8.

No new matter has been added by the amendments. Entry of the foregoing amendments and remarks is respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1-50, 58-64, 72-78 and 89-106 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner contends that it is unclear what is the definition of a common response motif. The Examiner also contends that it is unclear what is the content of the consensus profile. The Examiner further contends that it is unclear what are the metes and bounds of the sets of cellular constituents. Applicants have amended the claims to obviate the rejection.

Claim 1 has been amended to delete the term "common response motifs," thus obviating the rejection with respect to the term. Claim 1 has also been amended to particularly point out that the claimed method is for determining a consensus profile for *a first plurality of perturbations* by identifying *one or more sets of cellular constituents, each of said one or more sets of cellular constituents being upregulated or downregulated by said first plurality of perturbations* and that the consensus profile comprises measurements of *said one or more sets of cellular constituents* (emphasis added). Thus it is clear that the consensus profile comprises measurements of those sets of cellular constituents that are upregulated or downregulated by a group of perturbations, i.e., the first plurality of perturbations. To put it in another way, Applicants respectfully point out that the claimed method involves determining among, or picking out from, sets of co-varying or co-regulated cellular constituents one or more sets that have similar response to (i.e., upregulated or downregulated by) a group of perturbations (i.e., the first plurality of perturbations) and using the one or more sets as the consensus profile for this group of perturbations. Applicants further

respectfully point out that the sets of co-varying or co-regulated cellular constituents from which the one or more sets are picked out are determined independently, e.g., based on co-variation under a second plurality of perturbations. As a hypothetical example, if we have 500 response profiles each obtained from a sample under a different perturbations (i.e., 500 different perturbations) and if we have determined that the cellular constituents can be grouped into 100 sets for these response profiles, the claimed method may be used to identify e.g., 5 sets that are upregulated or downregulated by a group of e.g., 20 perturbations, and thus, measurements of these 5 sets constitute the consensus profile for the group of 20 perturbations. With respect to the definition of sets of cellular constituents, Applicants have amended the claim to recite that *each set of cellular constituents in said plurality of sets of cellular constituents* consists of cellular constituents that co-vary under a second plurality of perturbations or that are co-regulated. Thus, Applicants respectfully point out that in the claimed method *each set* of cellular constituents consists of cellular constituents that are co-varying or co-regulated. Therefore, Applicants respectfully submit that the rejection is obviated and should be withdrawn.

Claims 29, 38, 39 44, 58, 72 and 100 have also been amended to obviate the rejection. Applicants respectfully submit that the rejection with respect to these claims should be withdrawn.

For all the above reasons, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

THE REJECTION UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

Claims 1, 6, 10-13, 19-21, 27-34, 38, 44-46, 72-76, 89-91, 97, 98, and 100-102 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Hoffmaster et al., 1997, Infection and Immunity 65:3091-3099. The Examiner contends that Hoffmaster performs 2-D gel electrophoresis measurements of protein expression to obtain three response profiles from samples under four different perturbations[1] and identifies seven spots which constitute a consensus profile, thus Hoffmaster anticipates the presently claimed invention. The

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[1] In the Office Action dated November 22, 2000, the Examiner contends that four perturbations are shown. Applicants respectfully point out that Hoffmaster compares profiles from three instead of four perturbations, i.e., air growth with UM44 cells, 5% CO_2 with UM44 cells, and 5% CO_2 with UT53 cells (*atxA*$^-$).

Examiner also contends that the cluster analysis limitation is deemed to be met in Hoffmaster by the detection of co-varying clusters of gene products.

A claim is anticipated under 35 U.S.C. § 102 only if each and every element and limitation as set forth in the claim is found, either expressly described or inherently present, in a single prior art reference. *Glaxo, Inc. v. Novopharm Ltd.*, 52. F.3d 1043, 1047 (Fed. Cir. 1995). There must be *no differences* between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdn. v. Genentech, Inc.* 927 F. 2d. 1565, 1576 (Fed. Cir. 1991).

Hoffmaster teaches analysis of protein production in cells of *Bacillus anthracis* under three different conditions using 2-D gel electrophoresis. In Figs. 1a and 1b, Hoffmaster compares 2-D gel profiles of cell samples under air growth, 5% CO_2, and 5% CO_2 with *atxA*$^-$, and identifies seven protein species which are regulated by CO_2 and *atxA* (see Hoffmaster Fig. 1b). Thus Hoffmaster teaches only the comparison of proteins in three response profiles under three different conditions.

With respect to the rejection over claims 1, 44, 72 and 100, and the claims dependent thereon, Applicants have amended the claims to particularly point out that in the presently claimed methods, sets of cellular constituents and consensus profiles are determined from at least five response profiles. Hoffmaster does not teach determining consensus profiles from more than three response profiles. Thus, the rejection under 35 U.S.C. § 102(b) over claims 1, 44, 72, 100 and the claims dependent thereon based on Hoffmaster is obviated and should be withdrawn.

With respect to the rejection over claims 29 and 38, and the claims dependent thereon, Applicants respectfully point out that none of these claims are anticipated by Hoffmaster. Claim 29 teaches a method of determining a consensus profile from a plurality of projected profile. Nowhere does Hoffmaster teach a projected profile, much less determining a consensus profile from a plurality of projected profiles. In this regard, Applicants respectfully direct the attention of the Examiner to page 35, line 25 through page 36, line 30 and Section 5.3.4. in the specification for a description of projected profiles. Claim 38 teaches a method of determining a consensus profile that comprises measurements of transcript levels of genes. Hoffmaster teaches only profiles of proteins generated by 2-D gel electrophoresis. Nowhere does Hoffmaster teach expression profiles of measurements of

transcript levels of genes. Thus, the rejection under 35 U.S.C. § 102(b) over claims 29 and 38 and the claims dependent thereon based on Hoffmaster should be withdrawn.

With respect to the rejection over claims 101 and 102, Applicants respectfully point out that the claims relate to a method for grouping measured response profiles in sets by cluster analysis. The term "cluster analysis" as used in this application specifically refers to the methods described in Section 5.3.2 of the specification. For example, at page 23, lines 23-24, it is clearly disclosed that "by means of a cluster analysis" refers to "by means of a cluster algorithm." Thus, contrary to the Examiner's contention, the cluster analysis limitation is not met by detection of a cluster of gene products in 2-D gel experiments. Thus, the rejection under 35 U.S.C. § 102(b) over claims 101 and 102 based on Hoffmaster should be withdrawn.

Thus, Applicants submit that Hoffmaster does not anticipate the claimed methods of the present invention. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Withdrawal of the Examiner's rejections is respectfully requested.

Respectfully submitted,

Date May 22, 2001

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Adriane M. Antler (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosures

EXHIBIT A: MARKED VERSION OF AMENDED CLAIMS
U.S. APPLICATION SERIAL NO. 09/220,142
(ATTORNEY DOCKET NO. 9301-035-999)

(as amended May 22, 2001)

1. (Three Times Amended) A method of determining a consensus profile for a first plurality of perturbations to a cell type or organism, said method comprising identifying [common response motifs] among a plurality of sets of cellular constituents in a plurality of response profiles one or more sets of cellular constituents, each of said one or more sets of cellular constituents being upregulated or downregulated by said first plurality of perturbations, each response profile in said plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different perturbation to said type of cell or organism, wherein each [of said sets] set of cellular constituents in said plurality of sets of cellular constituents consists of cellular constituents that co-vary under a second plurality of perturbations or that are co-regulated, wherein said plurality of response profiles comprises at least five response profiles, and wherein said [common response motifs constitute the] consensus profile for said first plurality of perturbations comprises measurements of said one or more sets of cellular constituents.

2. (Canceled)

3. (Amended) The method of claim [2] 1, wherein the plurality of response profiles comprises more than ten response profiles.

6. (Twice Amended) The method of claim 1, wherein [the] said first plurality of perturbations are associated with a particular biological effect.

19. (Amended) The method of claim 1, wherein the [common response motifs] one or more sets of cellular constituents are identified by re-ordering the response profiles into sets associated with similar biological effects.

29. (Twice Amended) A method of determining a consensus profile for a first plurality of perturbations to a cell type or organism, said method comprising identifying

[common response motifs] among a plurality of sets of cellular constituents in a plurality of projected profiles one or more sets of cellular constituents, each of said one or more sets of cellular constituents being upregulated or downregulated by said first plurality of perturbations, each projected profile in said plurality of projected profiles

(i) resulting from a different perturbation to said type of cell or organism, and

(ii) comprising measurements of a plurality of cellular constituents in said type of cell or organism that have been projected onto basis cellular constituent sets, said basis cellular constituent sets being defined by co-variation of measurements of cellular constituents under a second plurality of different perturbations, wherein said [common response motifs constitute the] consensus profile for said first plurality of perturbations comprises projected measurements of said one or more sets of cellular constituents.

30. (Twice Amended) The method of claim 1 wherein the consensus profile is the intersection of the sets of cellular constituents activated or de-activated [in the common response motifs] by said first plurality of perturbations.

31. (Twice Amended) The method of claim 29, wherein the consensus profile is the intersection of the sets of cellular constituents activated or de-activated [on the common response motifs] by said first plurality of perturbations.

32. (Amended) The method of claim 30 or 31, wherein the [common response motifs] one or more sets of cellular constituents are identified by re-ordering the response profiles into sets associated with similar biological effects.

38. (Three times Amended) A method of determining a consensus profile for a first plurality of perturbations to a cell type or organism, said method comprising identifying [common response motifs] among a plurality of sets of genes in a plurality of response profiles one or more sets of genes, each of said one or more sets of genes being upregulated or downregulated by said first plurality of perturbations, each response profile in said plurality of response profiles (i) comprising measurements of transcript levels for a plurality of genes, and (ii) resulting from a different perturbation to said type of cell or organism, wherein each [of said sets] set of genes in said plurality of sets of genes consists of genes

having transcripts that co-vary under a second plurality of perturbations or that are co-regulated, and wherein said [common response motifs constitute the] consensus profile for said perturbations comprises measurements of transcript levels for said one or more sets of genes.

39. (Twice Amended) A method for comparing a biological response profile to a consensus profile, said consensus profile comprising [common response motifs among a plurality of projected response profiles] projected measurements of one or more sets of cellular constituents, said one or more sets having been identified among a plurality of sets of cellular consituents in a plurality of projected response profiles, each of said one or more sets of cellular constituents being upregulated or downregulated by a first plurality of perturbations, each projected response profile in said plurality of projected response profiles

(i) resulting from a different perturbation to said type of cell or organism, and

(ii) comprising measurements of a plurality of cellular constituents in said type of cell or organism that have been projected onto basis cellular constituent sets, said basis cellular constituent sets being defined by co-variation of measurements of cellular constituents under a second plurality of different perturbations, [wherein said common response motifs constitute the consensus profile for said of perturbations,] said method comprising:

(a) converting the biological response profile into a projected response profile by projecting measurements of cellular constituents in said biological response profile onto said basis cellular constituent sets; and

(b) determining the value of a similarity metric between the projected response profile and the consensus profile.

44. (Three Times Amended) A method for grouping measured response profiles in sets which are associated with similar biological effects comprising grouping response profiles [into sets] among a plurality of response profiles into sets, each of said sets of response profiles consisting of response profiles in which the responses of one or more sets of cellular constituents in each response profile are similar among response profiles in the set, each response profile in said plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different perturbation, wherein each of said sets of cellular constituents consists of cellular constituents that co-vary under a

plurality of perturbations or that are co-regulated, wherein said plurality of response profiles comprises at least five response profiles.

72. (Twice Amended) A method for analyzing response data from a biological sample comprising

(a) grouping cellular constituents from the biological sample into sets of cellular constituents that co-vary in a plurality of response profiles, each response profile in said plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different perturbation to said biological sample; and

(b) grouping the plurality of response profiles into sets of response profiles that similarly affect cellular constituents,

wherein said plurality of response profiles comprises at least five response profiles.

100. (Twice Amended) A method of grouping sets of perturbations that similarly affect cellular constituents in a cell type or organism among a plurality of perturbations comprising grouping response profiles among a plurality of response profiles in sets, each of said sets of response profiles consisting of response profiles in which the responses of one or more sets of cellular constituents are similar among the response profiles in the set, each response profile in said plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different perturbation, wherein each of said sets of cellular constituents consists of cellular constituents that co-vary under a plurality of perturbations or that are co-regulated, thereby grouping said sets of perturbations, wherein said plurality of response profiles comprises at least five response profiles.